Naloxone: Effects and Side Effects

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Naloxone: Effects and Side Effects

- Specificity
- Toxicology
- Unmasking Disease

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ARTICLE

doi:10.1038/nature10954

Crystal structure of the μ-opioid receptor bound to a morphinan antagonist

Aashish Manglik[1], Andrew C. Kruse[1], Tong Sun Kobilka[1], Foon Sun Thian[1], Jesper M. Mathiesen[1], Roger K. Sunahara[2], Leonardo Pardo[3], William I. Weis[1,4], Brian K. Kobilka[1] & Sébastien Granier[1,5]

Opium is one of the world's oldest drugs, and its derivatives morphine and codeine are among the most used clinical drugs to relieve severe pain. These prototypical opioids produce analgesia as well as many undesirable side effects (sedation, apnoea and dependence) by binding to and activating the G-protein-coupled μ-opioid receptor (μ-OR) in the central nervous system. Here we describe the 2.8 Å crystal structure of the mouse μ-OR in complex with an irreversible morphinan antagonist. Compared to the buried binding pocket observed in most G-protein-coupled receptors published so far, the morphinan ligand binds deeply within a large solvent-exposed pocket. Of particular interest, the μ-OR crystallizes as a two-fold symmetrical dimer through a four-helix bundle motif formed by transmembrane segments 5 and 6. These high-resolution insights into opioid receptor structure will enable the application of structure-based approaches to develop better drugs for the management of pain and addiction.

Opium extracts from the plant *Papaver somniferum* have been used

that it may be possible to develop safer and more effective therapeutic

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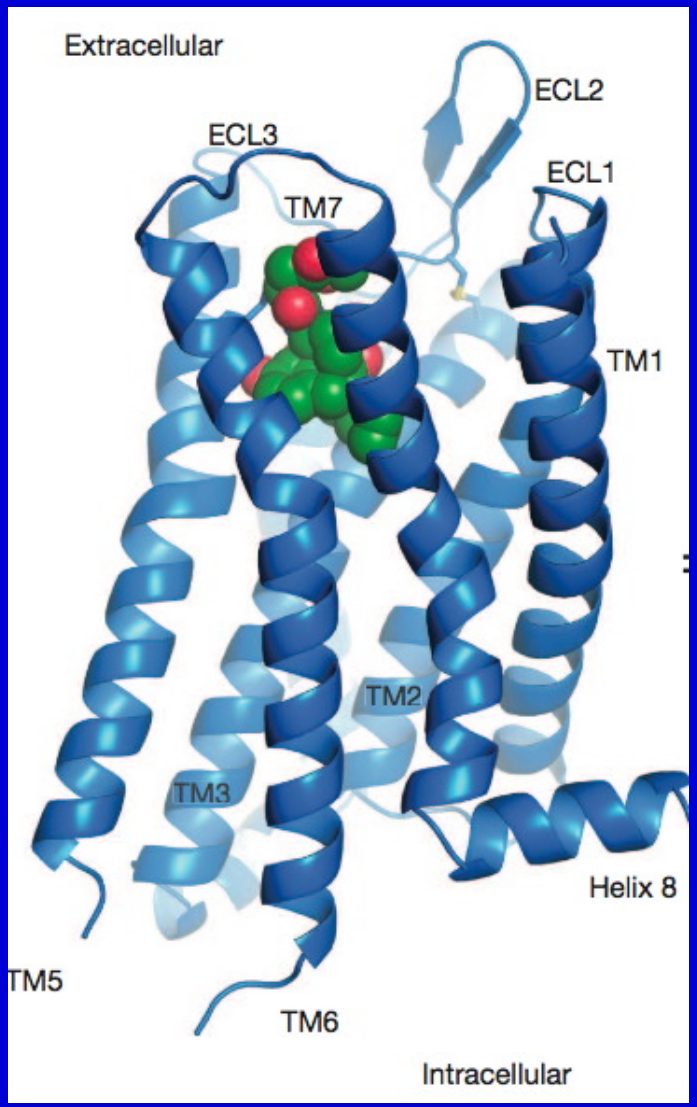

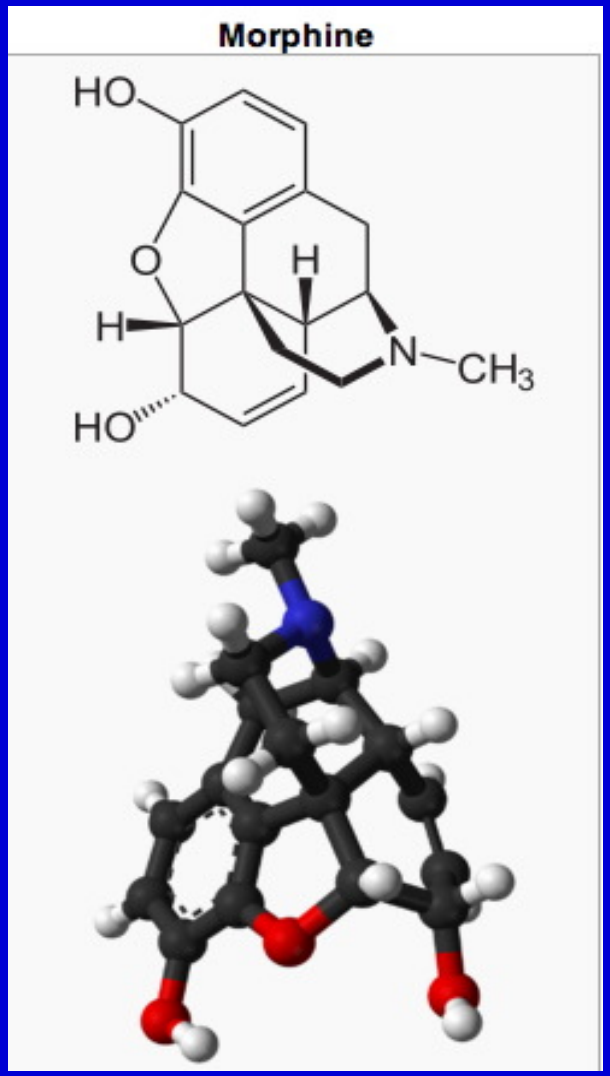

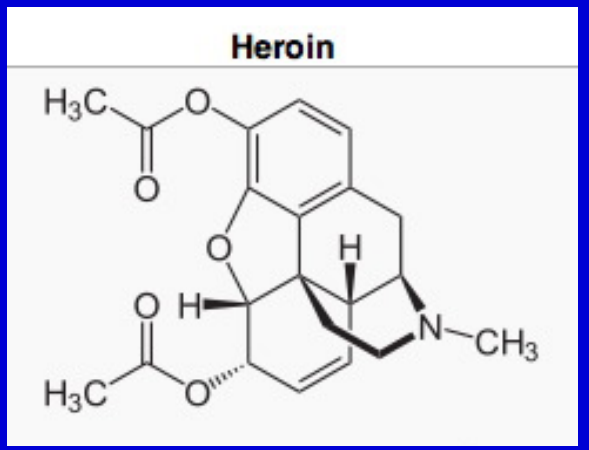

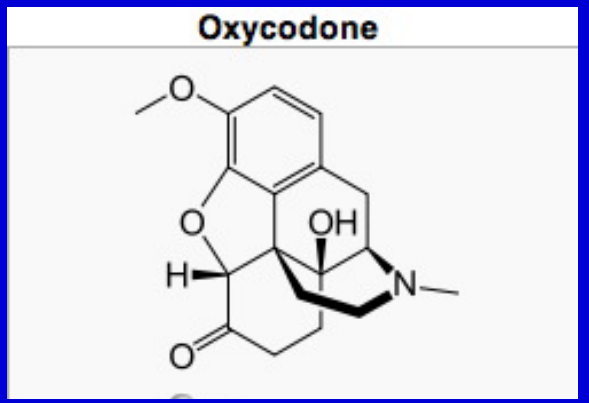

Naloxone: Effects and Side Effects

N-ALLYLNOROXYMORPHONE: A NEW POTENT NARCOTIC ANTAGONIST

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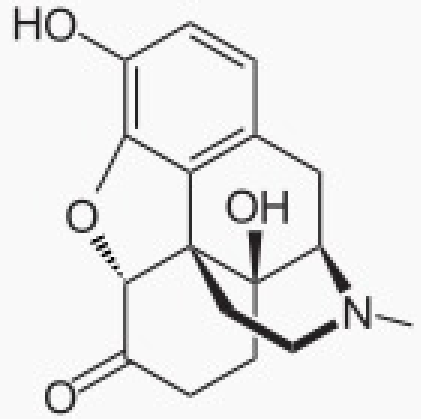
It has been known since 1915, when Pohl[17] described the antagonistic effect of N-allylcodeine on the codeine-induced respiratory depression that N-allyl derivatives of narcotic analgesics are capable of antagonizing narcotic-induced respiratory depression

production of controllable apnea during anesthesia (Foldes *et al.*[7]).

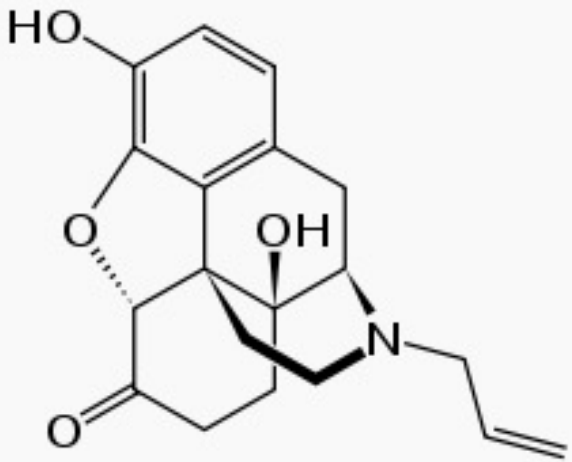
Recently the pharmacological effects of the N-allyl derivative of a potent narcotic analgesic, oxymorphone† (Numorphan (see Fig. 1), were investi-

Am. J. Med. Sci. 245: 23-30, 1963

Oxymorphone



Naloxone



Naloxone: Effects and Side Effects

Chapter 18. Opioids, Analgesia, and Pain Management

Tony L. Yaksh, Mark S. Wallace

< Previous Section | Next Section >

OPIOIDS, ANALGESIA, AND PAIN MANAGEMENT: INTRODUCTION

Pain is a component of virtually all clinical pathologies, and management of pain is a primary clinical imperative. Opioids are a mainstay of pain treatment, but rational therapy may involve, depending upon the pain state, one or more drug classes, such as NSAIDs, anticonvulsants, and antidepressants. The properties of these non-opioid agents are presented in Chapters 34, 21, and 15. This chapter focuses first on the biochemical, pharmacological, and functional nature of the opioid system that defines the effects of opioids on pain processing, gastrointestinal-endocrine-autonomic functions, and reward-addiction circuits. Subsequently, the chapter presents principles that guide the use of opioid and non-opioid agents in the management of clinical pain states.

Update

3/22/2012: Abuse-Deterrent Dosage Formulations

The term *opiate* refers to compounds structurally related to products found in opium, a word derived from *opos*, the Greek word for "juice," natural opiates being derived from the resin of the opium poppy, *Papaver somniferum*. Opiates include the natural plant alkaloids, such as morphine, codeine, thebaine, and many semisynthetic derivatives. An opioid is any agent, regardless of structure, that has the functional and pharmacological properties of an opiate. Endogenous opioids, many of which are peptides, are naturally occurring ligands for opioid receptors found in animals. The term *endorphin* is used synonymously with *endogenous opioid peptides* but also refers to a specific endogenous opioid, β-endorphin. The term *narcotic* was derived from the Greek word *narkotikos*, for "benumbing" or "stupor." Although narcotic originally referred to any drug that induced narcosis or sleep, the word has become associated with opioids and is often used in a legal context to refer to a variety of substances with abuse or addictive potential.

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Drug Monographs
Naloxone

Sections:

- Basics
- Indications & Usage
- Contraindications
- Warnings/Precautions
- Adverse Reactions
- Interactions
- Dosing
- Administration
- Pregnancy & Lactation
- **Clinical Pharmacology**
- Monitoring
- Patient Education
- Storage & Compatibility
- Additional Information
- References

Clinical Pharmacology

Mechanism of Action

Pure opioid antagonist that competes and displaces narcotics at opioid receptor sites

Pharmacokinetics

Onset of action: Endotracheal, I.M., SubQ: 2-5 minutes; Intranasal: ~8-13 minutes (Kelley, 2005; Robertson, 2009); I.V.: ~2 minutes

Duration: ~30-120 minutes depending on route of administration; I.V. has a shorter duration of action than I.M. administration; since naloxone's action is shorter than that of most opioids, repeated doses are usually needed

Distribution: Crosses placenta

Metabolism: Primarily hepatic via glucuronidation

Half-life elimination: Neonates: 3-4 hours; Adults: 0.5-1.5 hours

Excretion: Urine (as metabolites)

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REVIEW ARTICLE

Anesthesiology 2010; 112:226–38

David S. Warner, M.D., and Mark A. Warner, M.D., Editors

Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression

Albert Dahan, M.D., Ph.D.,* Leon Aarts, M.D., Ph.D.,* Terry W. Smith, Ph.D.†

CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Opioid treatment of pain is generally safe with 0.5% or less events from respiratory depression. However, fatalities are regularly reported. The only treatment currently available to reverse opioid respiratory depression is by naloxone infusion. The efficacy of naloxone depends on its own pharmacological charac-

opioid use have become well known and may be managed appropriately, with nausea, vomiting, sedation, and respiratory depression being associated commonly with postoperative analgesic doses. However, these side effects should not be trivialized. Postoperative nausea and vomiting is common and distressing

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interaction involving Mg liganding or hydrogen bonding via bridging water molecules as the major factors determining the relative orientations of the porphine rings[35,38,39]. Our new findings for this particular Bchl-protein indicate that interactions between chlorophyll and protein including liganding to the magnesium atom, hydrogen bonding and hydrophobic interactions are of major importance in determining the arrangement of the chlorophyll molecules. Furthermore we suggest that these types of interaction could be of universal significance in determining the state of chlorophyll *in vivo*.

Our results may be summarised as follows: the three-dimensional structure of a chlorophyll-containing protein has been determined by X-ray crystallography and shown to consist of three identical subunits, each containing a core of seven bacteriochlorophylls enclosed within an envelope of protein. The bacteriochlorophyll molecules are confined within a flattened disk-shaped region with their porphine rings lying roughly parallel to the disk. In contrast to current models for chlorophyll arrangement *in vivo*, the chlorophyll packing is dominated by interactions between chlorophyll and protein rather than between chlorophyll and lipid or between adjacent chlorophyll molecules. Furthermore the chlorophylls are arranged in an irregular fashion rather than in strictly ordered one-dimensional or two-dimensional arrays. It is suggested that the arrangement of chlorophyll seen here, in close association with protein, typifies the usual arrangement of chlorophyll *in vivo*.

We thank Dr J. M. Olson for supplying the bacteriochlorophyll protein and for his help, Dr S. Perez for help with data collection, Dr L. F. Ten Eyck for providing the Fourier transform and parameter refinement programs, S. J. Remington for the stereo-plotting program, and Dr L. H. Weaver, Mr W. R. Kester, Mrs H. F. Matthews and Ms J. Stephens for their assistance. This work was supported by grants from the US National Science Foundation and the National Institutes of Health. B. W. M. is an Alfred P. Sloan Research Fellow.

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1 Olson, J. M., and Romano, C. A., *Biochim. biophys. Acta*, **59**, 726–728 (1962).
2 Sybesma, C., and Olson, J. M., *Proc. natn. Acad. Sci. U.S.A.*, **49**, 248–253 (1963).
3 Sybesma, C., and Vredenberg, W. J., *Biochim. biophys. Acta*, **75**, 439–441 (1963).
4 Sybesma, C., and Vredenberg, W. J., *Biochim. biophys. Acta*, **88**, 205–207 (1964).
5 Thornber, J. P., and Olson, J. M., *Biochemistry*, **7**, 2242–2249 (1968).
6 Philipson, K. D., and Sauer, K., *Biochemistry*, **11**, 1880–1885 (1972).
7 Fenna, R. E., Matthews, B. W., Olson, J. M., and Shaw, E. K., *J. molec. Biol.*, **71**, 231–240 (1974).
8 Olson, J. M., Koenig, D. F., and Ledbetter, M. C., *Archs Biochem. Biophys.*, **129**, 42–48 (1969).
9 Matthews, B. W., Klopfenstein, C. E., and Colman, P. M., *J. Phys. E.*, **5**, 353–359 (1972).
10 Dickerson, R. E., Kendrew, J. C., and Strandberg, B. E., *Acta Crystallogr.*, **14**, 1188–1195 (1961).
11 Blow, D. M., and Crick, F. H. C., *Acta Crystallogr.*, **12**, 794–802 (1959).
12 North, A. C. T., *Acta Crystallogr.*, **18**, 212–216 (1965).
13 Matthews, B. W., *Acta Crystallogr.*, **20**, 82–86 (1966).

Identification of two rela the brain with potent opi

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Linda A. Fothergill
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Enkephalin, a natural ligand for opiate receptors is composed of the pentapeptides H–Tyr–Gly–Gly–Phe–Met–OH and H–Tyr–Gly–Gly–Phe–Leu–OH. The evidence is based on the determination of the amino acid sequence of natural enkephalin by the dansyl–Edman procedure and by mass spectrometry followed by synthesis and comparison of the natural and synthetic peptides.

TERENIUS and Wahlström[1,2] and Hughes[3] have described the existence of an endogenous substance in the brain which acts as an agonist at opiate receptor sites. We later characterised this substance, termed enkephalin, as a low molecular weight peptide[4]. Other workers[5] have also confirmed the presence of a substance in the brain that competes for opiate binding sites and this substance, although not completely characterised, seems similar to enkephalin. A further peptide with opiate agonist actions, larger and chemically dissimilar to enkephalin, has been discovered in the pituitary gland[6]. We have now found that enkephalin is composed of two pentapeptides which we have identified and synthesised.

Enkephalin was isolated from pig brains as previously

guinea pig intestine. In each case a crucial item of evidence was that the effects of morphine and of the morphine-like compound in brain extracts could be blocked by low concentrations of specific morphine antagonists such as naloxone. Using these test systems

opiate

brain seems to interact strongly with the opiate receptors, suggesting that the mode of action of these drugs does not involve any of these known mech-

been used successfully by Terenius and Wahlstrom (*Acta physiol. scand.*, **94**, 74; 1975) and by Pasternak, *et al.* (*Life Sci.*, **16**, 1765; 1975), who have also

tic materials shown to mimic the ions of naturally occurring enphalin on the guinea pig ileum and use vas deferens preparations. Metkephalin is effective at very low conntrations on the mouse vas deferens, which it is about twenty times more tent than the powerful opiate agonist rmorphine. It is also some three times more potent than morphine in a ligand binding assay. Leu-Enkephalin is somewhat less potent than the methionine analogue.

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Toxicology in Rats:

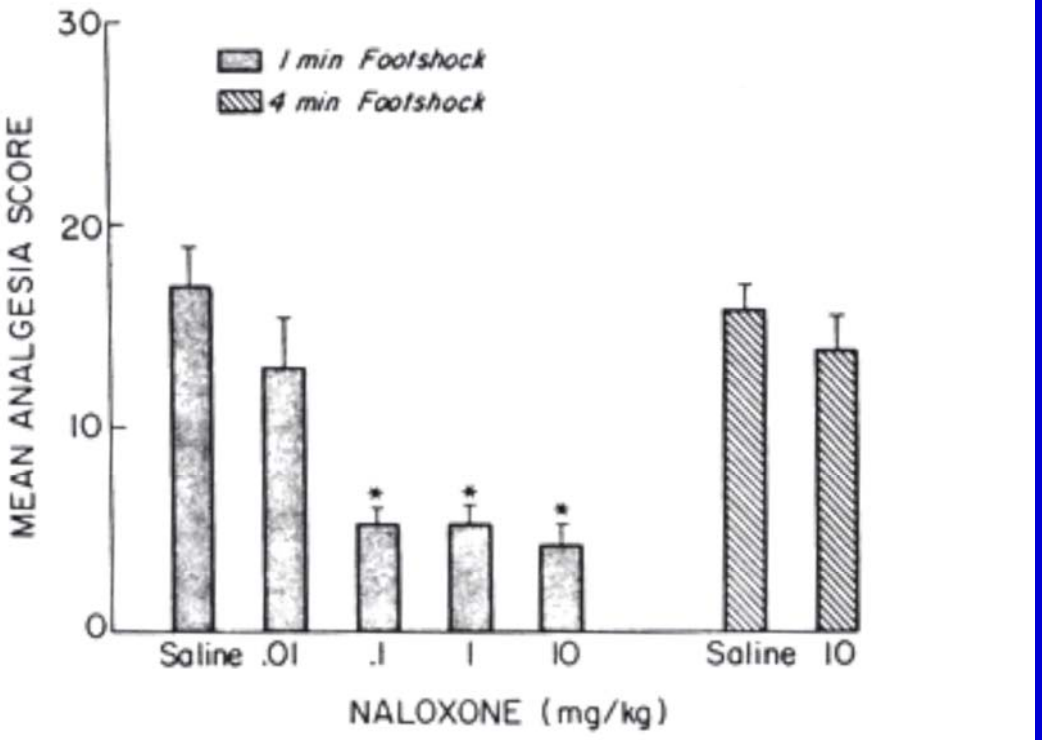

FIGURE 2: Dose-dependent reduction of 1 min stress analgesia but not 4 min stress analgesia by naloxone.
*Significantly different from saline controls ($p < 0.05$).

Naloxone: Effects and Side Effects

Toxicology in People:

- Packaged 0.4 mg/ml and recommended at 0.4-0.8 mg IV.
- We treat opiate overdose in hospital with 0.04 mg IV with repeated doses q2 min as necessary.
- In opiate naïve patients without pain IV doses up to 5.4 mg/kg boluses and 4 mg/kg/h have been administered without adverse effects (Clarke et al., Emerg Med J 22: 616-616, 2005) (although mild elevations in blood pressure and decreased performance on memory tests have been reported with doses over 20 mg)

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Naloxone: Effects and Side Effects

Drug Monographs
Naloxone

Sections:

Warnings/Precautions

Concerns related to adverse effects:

- Acute opioid withdrawal: May precipitate symptoms of acute withdrawal in opioid-dependent patients, including pain, hypertension, sweating, agitation, irritability; in neonates: shrill cry, failure to feed. Carefully titrate dose to reverse hypoventilation; do not fully awaken patient or reverse analgesic effect (postoperative patient).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or in patients receiving medications with potential adverse cardiovascular effects (eg, hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using narcotic antagonists. Administration of naloxone causes the release of catecholamines; may precipitate acute withdrawal or unmask pain in those who regularly take opioids.

- Seizures: Use caution in patients with history of seizures; avoid use in treatment of meperidine-induced seizures.

Other warnings/precautions:

- Opioid overdose: Recurrence of respiratory depression is possible if the opioid involved is long-acting; observe patients until there is no reasonable risk of recurrent respiratory depression.

- Postoperative reversal: Appropriate use: Excessive dosages should be avoided after use of opiates in surgery. Abrupt postoperative reversal may result in nausea, vomiting, sweating, tachycardia, hypertension, seizures, and other cardiovascular events (including pulmonary edema and arrhythmias).

Naloxone: Effects and Side Effects

Addiction (1994) 89, 1471–1475

Opiate withdrawal

MICHAEL FARRELL

National Addiction Centre, 4 Windsor Walk, London SE5 8AF, UK

Abstract

Opiate withdrawal is one of the longest studied and most well described withdrawal syndromes. Opiate withdrawal has been described as akin to a moderate to severe flu-like illness. Opiate withdrawal is appropriately described as subjectively severe but objectively mild. This paper describes the mechanisms of opiate dependence and opiate withdrawal and reviews the available instruments for the measurement of withdrawal. The time course of assisted and unassisted withdrawal is described and the range of options for the management of assisted withdrawal are described. This review concludes that the most effective and least time- and resource-consuming approach to opiate withdrawal will substantially contribute to the overall social management of opiate dependence.

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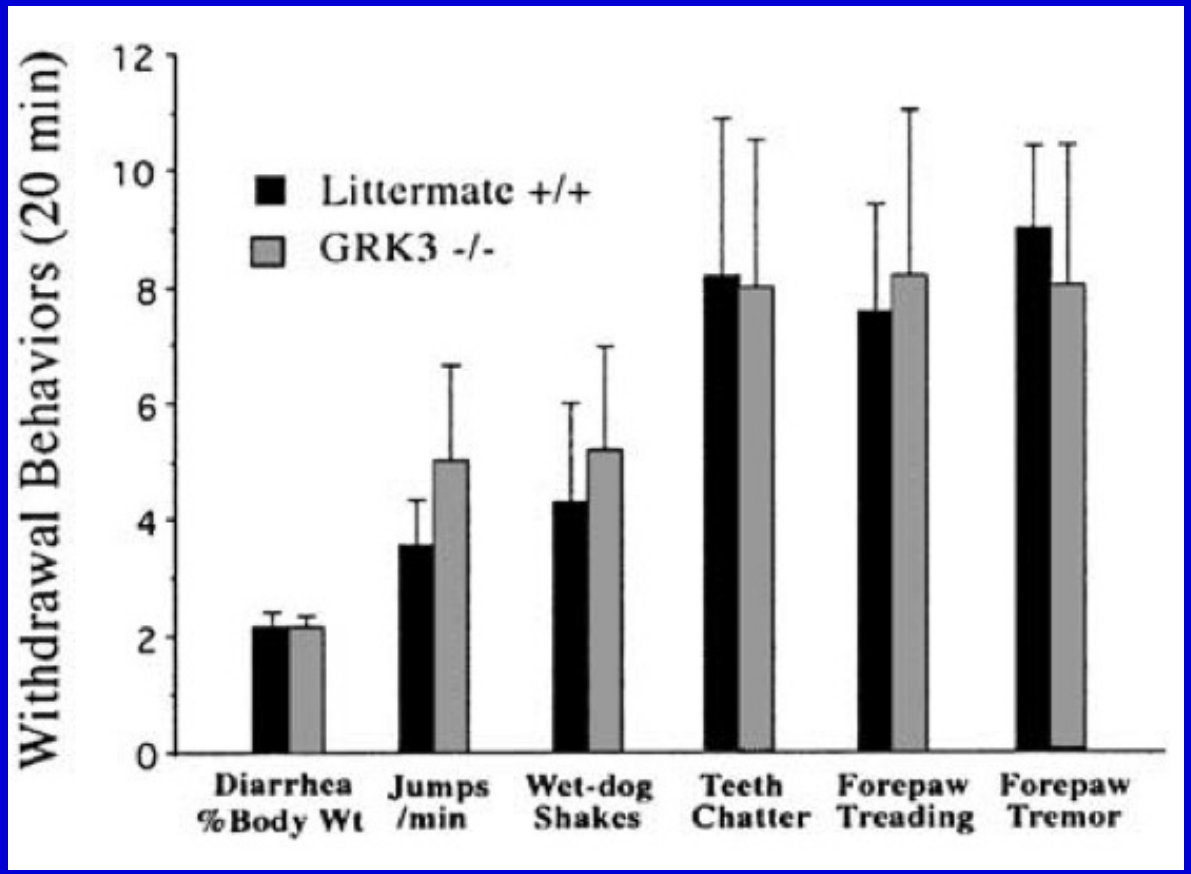
Opiate Withdrawal:



Terman et al, British Journal of Pharmacology, 2004

Symptoms

Early symptoms of withdrawal include:

- Agitation
- Anxiety
- Muscle aches
- Increased tearing
- Insomnia
- Runny nose
- Sweating
- Yawning

Late symptoms of withdrawal include:

- Abdominal cramping
- Diarrhea
- Dilated pupils
- Goose bumps
- Nausea
- Vomiting

Naloxone: Effects and Side Effects

Adverse events after naloxone treatment of episodes of suspected acute opioid overdose

Ingebjørg Buajordet[a], Anne-Cathrine Næss[b], Dag Jacobsen[c] and Odd Brørs[a]

Table 3. Events reported after naloxone treatment.

Events	No. of events (%) $n=726$
Confusion[a]	235 (32)
Headache[a]	157 (22)
Nausea/vomiting[a]	66 (9)
Aggressiveness[a]	62 (8)
Tachycardia[a]	47 (6)
Shivering	33 (5)
Seizures[a]	27 (4)
Sweating	24 (3)
Tremor	9 (1)
Miscellaneous	66 (9)

[a]Predefined events noted in the reporting charts used by the paramedics.

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Results:

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Drug Monographs
Naloxone

Sections:

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Naloxone: Effects and Side Effects

Cardiovascular effects

- Withdrawal induced catecholamine release (e.g., sweating)
  - Tachycardia or other arrhythmia (myocardial ischemia) morbidity
    - In patients with other drugs on board (e.g., cocaine)
    - In patients with pre-existing cardiac disease
    - In patients with hypoxia and/or hypercarbia

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American Journal of Emergency Medicine (2008) **26**, 113.e5–113.e8

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The American Journal of Emergency Medicine

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Case Report

Should naloxone be prescribed in the ED managem patients with cardiac arrest? A case report and rev literature☆

Abstract

We report the case of a patient in cardiac arre persistent pulseless electrical activity despite c treatment, who returned to spontaneous circulatio after the administration of naloxone. It is possib naloxone may have a role in pulseless electrical a asystole related to opioid intoxication and, perha cardiac arrest related to hypoxia.

Opioid intoxication is a frequent cause of r

Resuscitation 81 (2010) 42–46

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Resuscitation

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Clinical paper

Naloxone in cardiac arrest with suspected opioid overdoses☆

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ABSTRACT

Introduction: Naloxone's use in cardiac arrest has been of recent interest, stimulated by conflicting results in both human case reports and animal studies demonstrating antiarrhythmic and positive ionotropic effects. We hypothesized that naloxone administration during cardiac arrest, in suspected opioid overdosed patients, is associated with a change in cardiac rhythm.

Methods: From a database of 32,544 advanced life support (ALS) emergency medical dispatches between

Naloxone: Effects and Side Effects

Cardiovascular effects

- Withdrawal induced catecholamine release (e.g., sweating)
  - Tachycardia or other arrhythmia (myocardial ischemia) morbidity
    - In patients with other drugs on board (e.g., cocaine)
    - In patients with pre-existing cardiac disease
    - In patients with hypoxia and/or hypercarbia
  - Hypertension morbidity (e.g., vascular aneurysms)
    - Pulmonary edema (e.g., in heart failure)

Naloxone: Effects and Side Effects

Naloxone-Induced Pulmonary Edema

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Received for publication November 21, 1986. Revision received April 27, 1987. Accepted for publication June 16, 1987.

Address for reprints: Max D Koenigsberg, MD, Department of Emergency Medicine, Illinois Masonic Medical Center, 836 West Wellington Avenue, Chicago, Illinois 60657.

We present the case of a 68-year-old woman with acute pulmonary edema secondary to the administration of naloxone to reverse an inadvertent narcotic overdose. The patient presented following a 12-hour history of increasingly bizarre behavior and confusion. A total IV dose of 1.6 mg naloxone was administered in an attempt to reverse the suspected overconsumption of a codeine-containing cough suppressant. She immediately became agitated, tachycardic, and diaphoretic; a clinical diagnosis of acute pulmonary edema was made. Following treatment with furosemide, nitroglycerin, and morphine sulfate, the patient recovered completely without further incident. Although naloxone is thought to be a safe drug with few complications, it should not be used indiscriminantly, and the smallest doses necessary to elicit the desired response should be used. [Schwartz JA, Koenigsberg MD: Naloxone-induced pulmonary edema. Ann Emerg Med November 1987;16:1294-1296.]

INTRODUCTION

Naloxone is an opiate antagonist without intrinsic agonist activity used for the reversal of narcotic-induced respiratory depression and in the diagnosis of suspected acute opiate overdosage. While being structurally similar to oxymorphine, it is essentially a pure narcotic antagonist that counteracts the effects of narcotics, including respiratory depression, coma, analgesia, pupillary constriction, seizures, and cardiovascular and gastrointestinal effects. Naloxone may precipitate withdrawal symptoms in individuals with physical narcotic dependency. In general, naloxone is widely accepted to be a benign drug with few adverse side effects or contraindications.

We present a case of acute pulmonary edema after naloxone administration, an unusual adverse reaction previously unreported in the emergency medicine literature.

CASE REPORT

A 68-year-old woman was brought to the emergency department because

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Acta Anaesthesiol Taiwan 2010;48(3):155–157

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CASE REPORT

Negative Pressure Pulmonary Edema Following Naloxone Administration in a Patient With Fentanyl-induced Respiratory Depression

Huei-Chi Horng[1], Min-Tzung Ho[2], Chih-Hung Huang[1], Chun-Chang Yeh[3], Chen-Hwan Cherng[3]*

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Revised: Nov 9, 2009
Accepted: Nov 12, 2009

Naloxone is commonly used to reverse narcotic intoxication. However, its use is not entirely free of hazards. For instance, pulmonary edema (PE) has been reported to arise with the mechanism of over-sympathetic discharge caused by release of cat-

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Negative Pressure Pulmonary Edema after Acute Upper Airway Obstruction

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Charbel A. Kenaan, MD,† Alex M. Barrocas, MS,‡
Janett J. Fonseca, MD,† George B. Bikazi, MD§

Department of Anesthesiology, University of Miami School of Medicine, and Department of Anesthesiology, Jackson Memorial Medical Center, Miami, FL, and University of Medicine and Dentistry of New Jersey, Newark, NJ.

Study Objectives: *To review the clinical characteristics and the pathogenesis of negative pressure pulmonary edema, and to determine its incidence in surgical patients.*
Design: *Retrospective case-report study.*
Setting: *Operating room, postanesthesia care unit and surgical intensive care of a teaching hospital.*
Patients: *30 surgical adult ASA physical status I, II, III, IV, and V patients who suffered from negative pressure pulmonary edema during the period 1992–1995.*
Measurements and Main Results: *This study showed a rapid onset of negative pressure pulmonary edema after acute upper airway obstruction, due mainly to laryngospasm in the postoperative period and to upper airway pathology in the preoperative period. Negative pressure pulmonary edema appeared more frequent in healthy (ASA physical status I and II), middle-aged and male patients, with a general incidence of 0.094%. The resolution was relatively rapid after reestablishment of the airway, adequate oxygenation, and positive airway pressure application. The clinical course was uncomplicated in all the patients.*
Conclusions: *In this study, negative pressure pulmonary edema presented a relatively high incidence. Prevention, early diagnosis, and prompt treatment allowed a rapid and uncomplicated resolution.* © 1997 by Elsevier Science Inc.

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Introduction

The link between acute upper airway obstruction and pulmonary edema was suggested in the late 1920's in animal models.[1] Despite the fact that the pathophysiology of this association began to be understood in the early 1940's, it was not until 1977 that the first case report of pulmonary edema following laryngospasm was published.[2] Even today an underreporting of the cases of negative pressure pulmonary edema (NPPE), after acute upper airway obstruction, still exists.

After a short review of the pathophysiology of NPPE, the results of this case report study, which was performed in 30 adult patients who developed NPPE after acute upper airway obstruction from 1992 to 1995, are discussed.

Materials and Methods

From a total of 31,826 adult patients scheduled for surgery during the period 1992–1995, at Jackson Memorial Hospital-University of Miami, 30 cases of NPPE were reported. The hospital records of these patients and the postanesthesia

Naloxone: Effects and Side Effects

Cardiovascular effects

- Withdrawal induced catecholamine release (e.g., sweating)
  - Tachycardia or other arrhythmia (myocardial ischemia) morbidity
    - In patients with other drugs on board (e.g., cocaine)
    - In patients with pre-existing cardiac disease
    - In patients with hypoxia and/or hypercarbia
  - Hypertension morbidity (e.g., vascular aneurysms)
    - Pulmonary edema (e.g., in heart failure) – perhaps most commonly post-obstructive

Naloxone: Effects and Side Effects

Seizure effects

- May lower seizure thresholds for patients with prior seizure disorder or immediately post-ictal (i.e., after a seizure).

Naloxone: Effects and Side Effects

Clinical Toxicology, 34(4), 409–416 (1996)

Naloxone—For Intoxications with Intravenous Heroin and Heroin Mixtures—Harmless or Hazardous? A Prospective Clinical Study

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ABSTRACT

Background: Naloxone is standard medication for the treatment of heroin intoxications. No large-scale studies have yet been carried out to determine its toxicity in heroin intoxications. Methods: We have undertaken an investigation as to the frequency, type and degree of severity of complications attributable to naloxone administration. Subjects treated between 1991 and 1993 with naloxone for intravenous drug intoxications were prospectively evaluated. Main Outcome Measurements: Development of ventricular tachycardia or fibrillation; atrial fibrillation; asystole; pulmonary edema; convulsions; vomiting; and violent behavior within ten minutes after parenteral administration of naloxone. Results: Six of 453 intoxicated subjects (1.3%; 95% confidence interval 0.4%-3%) suffered severe adverse effects within ten minutes after naloxone administration (one asystole; three generalized convulsions; one pulmonary edema; and one violent behavior). After the ten minute period, no further complications were observed. Conclusions: The short time between naloxone administration and the occurrence of complications, as well as the type of complications, are strong evidence of a causal link. In 1000 clinically diagnosed intoxications with heroin or heroin mixtures, from 4 to 30 serious complications can be expected. Such a high incidence of complications is unacceptable and could theoretically be reduced by artificial respiration with a bag valve device (hyperventilation) as well as by administering naloxone in minimal divided doses, injected slowly.

Table 4

Complications after Naloxone Administration

Case	Events	Sex	Age y	Intoxication	Naloxone mg	Survival	Status Pre-naloxone
1	asystole	M	21	heroin/cocaine/ cannabis*	0.4	yes	rhabdomyolysis CK 49,200 mmol/L K 5.1 mmol/L aspiration
2	violent behavior	M	31	heroin*	?	yes	Graves' disease
3	pulmonary edema	M	31	heroin/ flunitrazepam*	0.2	yes	hypothermia 30° C K 6.0 mmol/L glucose 27.9 mmol/L rhabdomyolysis, mild
4	generalized convulsion	M	19	heroin/ flunitrazepam*	1	yes	suicidal attempt
5	generalized convulsion	M	31	heroin/alcohol*	0.8	no	asystole in ED; hypoxemic encephalopathy; hyperthermia 40°C
6	generalized convulsion	M	31	heroin	0.3	yes	epilepsy

Naloxone: Effects and Side Effects

Brain Research, 167 (1979) 435–440

Endogenous opioids may
daloid-kindled rats

HANAN FRENK, JEROME EN
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Departments of Neurology and
Medicine and Department of Psych

(Accepted January 11th, 1979)

Intraventricular injecti
doses of morphine cause mar
EEG of rats accompanied by myoclonic twitches and 'wet-dog' shakes[6,16]. These

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Nucleus accumbens μ opioid receptors mediate immediate postictal decrease in locomotion after an amygdaloid kindled seizure in rats

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ABSTRACT

Postictal movement dysfunction is a common symptom in patients with epilepsy. We investigated the involvement of opioid receptors in the nucleus accumbens (NAC) in amygdaloid kindling-induced postictal decrease in locomotion (PDL) in rats. Seizures were induced by daily electrical stimulation of the basolateral amygdala until four consecutive stage 5 seizures were elicited. Locomotion was quantified before and after infusion of an opioid receptor antagonist or saline into the NAC. Whereas PDL was induced after a stage 5 seizure in saline-infused rats, pre-infusion of the μ opioid receptor antagonist H-D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2 (CTAP, 5 μg/1 μL/side) into the NAC prevented PDL. Pre-infusion of δ (naltrindole, 30 μg/1 μL/side), κ (*nor*-binaltorphimine, 1.8 μg/1 μL/side), or nonselective (naloxone, 10 μg/1 μL/side) opioid receptor antagonists did not block PDL, but late postictal hyperactivity

Naloxone: Effects and Side Effects

Seizure effects

- Theoretically, may lower seizure thresholds for patients with prior seizure disorder or immediately post-ictal (i.e., after a seizure).
- May unmask seizures from other drugs on board (e.g., cocaine).
- May unmask seizures due to hypoxia or hypercarbia.

Naloxone: Effects and Side Effects

Carbon Dioxide Narcosis and Grand Mal Seizure Complicating Laparoscopic Herniorrhaphy

Quentin M. Nunes, MS, MRCS, Elizabeth H. Gemmill, MRCS, Joanne R. Eastwood, BMBS, FRCA, and Dileep N. Lobo, DM, FRCS

Abstract: A 60-year-old man without comorbidity underwent a totally extraperitoneal repair of bilateral inguinal hernias under general anesthesia. Forty minutes after the procedure he developed a slow, shallow respiratory pattern with a respiratory rate of 5/min and a self-limiting grand mal seizure lasting 30 seconds. Arterial blood gas analysis indicated significant hypercarbia and acidosis. The total dose of morphine administered was 20 mg intravenously. Naloxone was administered and the respiratory rate improved. The patient was discharged after 24 hours after making a good recovery and has had no further seizures a year after surgery. Although hypercarbia is a well-known complication of laparoscopic surgery when CO_2 is used for insufflation, this, to the best of our knowledge, is the first reported case of a patient sustaining a grand mal seizure resulting from CO_2 narcosis after laparoscopic surgery. The possible mechanisms are discussed.

Key Words: carbon dioxide, complications, hypercarbia, laparoscopic surgery, seizures, totally extraperitoneal hernia repair

(*Surg Laparosc Endosc Percutan Tech* 2007;17:52–53)

Although the use of carbon dioxide (CO_2) to create and maintain a pneumoperitoneum or pneumoextraperitoneum in laparoscopic surgery is well established, there is a small but significant risk of complications such as hypercarbia, subcutaneous emphysema, decreased pulmonary compliance and vital capacity, and cardiovascular effects such as a diminished cardiac index and increased systemic vascular resistance. Totally extraperitoneal (TEP) laparoscopic inguinal hernia repair involves insufflation of CO_2 in the preperitoneal space (pneumopreperitoneum). We report a case of hypercarbia associated with seizures in a patient who underwent a TEP repair of bilateral inguinal hernias.

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Author contributions: Quentin M. Nunes: Data collection, writing of manuscript. Elizabeth H. Gemmill: Data collection, writing of manuscript. Joanne R. Eastwood: Critical revision of manuscript, approval of final version, supervision. Dileep N. Lobo: Critical revision of manuscript, approval of final version, supervision.
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CASE HISTORY

A 60-year-old man without comorbidity underwent an elective TEP repair of bilateral inguinal hernias under general anesthesia. A pneumopreperitoneum was created and maintained at a pressure of 10 mm Hg, and 3 laparoscopic ports were used. The total operative time was 1 hour 15 minutes and there were no intraoperative anesthetic complications (maximum end tidal CO_2 recorded was 10.0 kPa). The respiratory rate of the patient varied between 16 and 25/min during the procedure. The patient was transferred to the recovery area with the laryngeal mask airway in situ. However, 40 minutes after the procedure he developed a slow, shallow respiratory pattern with a respiratory rate of 5/min and a self-limiting grand mal seizure lasting 30 seconds. Clinically, the patient had subcutaneous emphysema extending up to his neck. An arterial blood gas analysis (Table 1), at the time indicated significant hypercarbia and acidosis. The total dose of morphine administered was 20 mg intravenously (the last dose being given at least 30 minutes before the seizure). Naloxone was administered and the respiratory rate improved. The patient was discharged after 24 hours after making a good recovery and has had no further seizures a year after surgery.

COMMENT

Although hypercarbia is a well-known complication of laparoscopic surgery when CO_2 is used for insufflation, this, to the best of our knowledge, is the first reported case of a patient sustaining a grand mal seizure resulting from CO_2 narcosis after laparoscopic surgery. Liem et al[1] have shown that pneumopreperitoneum for laparoscopic herniorrhaphy results in a rapid increase in $PaCO_2$ and a consequent decrease in pH. This can be explained by the fact that CO_2 absorption is more extensive in the preperitoneal space, because of a larger gas exchange area as a result of the absence of a natural border which allows diffusion of CO_2 into the subcutaneous tissues and the scrotum (as opposed to a pneumoperitoneum).[1] Lateral dissection for placement of the mesh during the repair also increases the total gas exchange area.[2] The large pressure gradient for CO_2 as a result of the larger gas exchange area and shorter anatomic distance results in an increased influx of CO_2 into the circulation.[1] Hypercarbia further stresses the cardiovascular system which is already compromised by decreased venous return

Naloxone: Effects and Side Effects

Drug Monographs
Naloxone

Sections:

Warnings/Precautions

Concerns related to adverse effects:

- Acute opioid withdrawal: May precipitate symptoms of acute withdrawal in opioid-dependent patients, including pain, hypertension, sweating, agitation, irritability; in neonates: shrill cry, failure to feed. Carefully titrate dose to reverse hypoventilation; do not fully awaken patient or reverse analgesic effect (postoperative patient).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or in patients receiving medications with potential adverse cardiovascular effects (eg, hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using narcotic antagonists. Administration of naloxone causes the release of catecholamines; may precipitate acute withdrawal or unmask pain in those who regularly take opioids.

- Seizures: Use caution in patients with history of seizures; avoid use in treatment of meperidine-induced seizures.

Other warnings/precautions:

- Opioid overdose: Recurrence of respiratory depression is possible if the opioid involved is long-acting; observe patients until there is no reasonable risk of recurrent respiratory depression.

- Postoperative reversal: Appropriate use: Excessive dosages should be avoided after use of opiates in surgery. Abrupt postoperative reversal may result in nausea, vomiting, sweating, tachycardia, hypertension, seizures, and other cardiovascular events (including pulmonary edema and arrhythmias).

Naloxone: Effects and Side Effects

No Deaths Associated with Patient Refusal of Transport After Naloxone-Reversed Opioid Overdose

Prehosp Emerg Care. 1999 Ju

Are heroin overd ... **h naloxone?**

Vilke GM, Buchanan J, Dur

Department of Emergency Me

Abstract

OBJECTIVE: Naloxone is ... authors' EMS system has operated a policy of ... field. This study was performed to evaluate the

METHODS: The authors ... id overdoses contributed to the cause of death. Th ... departments of reasons other than natural causes ... s a cause of death were cross-compared with all ... viewed by dates, times, age, sex, location, and, v

RESULTS: There were 1 ... fused further treatment. When compared by age, ... edics with naloxone within 12 hours of being f

CONCLUSIONS: Giving ... no death in the one-year period studied. This stud ... by private vehicles.

ical Examine ... 15:320–324 were treated

BRIEF REPORTS

Assessment for Deaths in Out-of-hospital Heroin Overdose Patients Treated with Naloxone Who Refuse Transport

Gary M. Vilke, MD, Christian Sloane, MD, Alan M. Smith, MPH, Theodore C. Chan, MD

Abstract

Naloxone frequently is used to treat suspected heroin and opioid overdoses in the out-of-hospital setting. The authors' emergency medical services system has operated a policy of allowing these patients, when successfully treated, to sign out against medical advice (AMA) in the field. **Objectives:** To evaluate the safety of this AMA policy. **Methods:** This is a retrospective review of out-of-hospital and medical examiner (ME) databases over a five-year period. The authors reviewed all ME cases in which opioid overdoses were listed as contributing to the cause of death. These cases were cross-compared with all patients who received naloxone by field paramedics and then refused transport. The charts were reviewed by dates, times, age, sex, location, and ethnicity when available. **Results:** There were 998 out-of-hospital patients who received naloxone and refused further treatment and 601 ME cases of opioid overdose deaths. When compared by age, time, date, sex, location, and ethnicity, there were no cases in which a patient was treated by paramedics with naloxone within 12 hours of being found dead of an opioid overdose. **Conclusions:** Giving naloxone to patients with heroin overdoses in the field and then allowing them to sign out AMA resulted in no identifiable deaths within this study population.

Key words: out-of-hospital; naloxone (Narcan); release; against medical advice; paramedic. ACADEMIC EMERGENCY MEDICINE 2003; 10:893–896.

In many emergency medical services (EMS) systems, a patient given naloxone (Narcan) for heroin overdose ... 1), the patient can be released AMA at the scene by paramedics without base hospital contact.[2] Although

Naloxone: Effects and Side Effects

Clinical Toxicology, 36(1&2), 11–17 (1998)

Opioid Toxicity Recurrence After an Initial Response to Naloxone

William A. Watson; Mark T. Steele;
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University of Missouri—Kansas City; Truman Medical Center, Kansas City, Missouri

ABSTRACT

Objective: To determine the frequency and potential predictors of opioid toxicity recurrence after a response to naloxone in adult Emergency Department patients. Methods: A retrospective case-control study of naloxone-treated patients with opioid toxicity over an 8-year period. Both the patient response to naloxone and recurrence of opioid toxicity was determined by an expert Delphi Panel. The frequency of opioid toxicity recurrence was compared by the duration of opioid effect, the route of opioid exposure, and the presence of other CNS depressant drugs. Results: Ninety of 221 (41%) cases with a discharge diagnosis of opioid toxicity were treated with naloxone; six patients were excluded because of a lack of toxicity. There was a response to naloxone in 50% of the 84 cases, and recurrence of toxicity in 31% (95% CI 17–45%) of naloxone responders. The most common opioids were codeine, heroin, propoxyphene, and oxycodone/hydrocodone. Recurrence of toxicity was more common with long-acting opioids ($p = 0.04$), and was not associated with the route of opioid exposure ($p = 0.42$), or presence of ethanol and other CNS depressants ($p \geq 0.87$). Conclusion: Opioid toxicity recurrence after a response to naloxone occurred in approximately 1/3 of adult Emergency Department opioid overdose cases. Recurrence was more common with long-acting opioids and was not associated with the route of opioid exposure. Other clinically useful predictors of toxicity recurrence were not identified.

Naloxone: Effects and Side Effects

- Specificity (Amazing)
- Toxicology (Forgiving)
- Unmasking Disease: Concerns
  - Opiate Dependence (Withdrawal)
  - Co-ingested Substances
  - Hypoxemia/Hypercarbia
    - Arrythmias
    - Seizures
  - Post-Obstructive Pulmonary Edema
  - Unrecognized Re-narcotization (perhaps worse with long–acting prescription meds than with other opiates)
  - Pain